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Cancer of the Melanocytic System

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Most skin cancer among caucasians is associated with exposure to sunlight (1), and damages to cellular DNA are implicated as initiating events because repair-deficient individuals (xeroderma pigmentosum) are orders of magnitude more susceptible than normal individuals. Within reasonably homogenous populations, skin cancer increases toward low latitudes, but this association does not indicate the wavelength regions involved in cancer induction. At present, the only animal model suitable for determining the wavelengths effective in melanoma induction are certain inter- and intraspecies hybrids of the small fish, Xiphophorus. Genetic evidence indicates that the hybrids contain only one tumor suppressor gene and, therefore, are very sensitive to cancer induction by single exposures to light (2). I and my colleagues (3) exposed 5-day old fish, in spectrophotometer cuvettes, to different monochromatic wavelengths and fluences. The fish were kept for two months in tanks shielded with yellow plastic, so as to minimize the possibility of photoreactivation, and were scored at four months. The melanoma prevalence increased with exposure to a maximum of ~ 0.5 (Fig. 1). The fluence-response curves were fitted to surviving fraction = $a+b(1-e^{-kE})$, where a is the background prevalence with no exposure, b is the maximum induced prevalence, k is the sensitivity parameter (the cross section for melanoma induction), and E is the incident fluence. The value of k at 302 nm was 0.05 m^2/J giving a mean melanoma inducing exposure, for swimming fish, of 200 J/m^2, corresponding to 3.5 cyclobutane pyrimidine dimers per Mbp of DNA in irradiated fish skin. At this wavelength the mean erythemal dose for a stationary human is 400 J/m^2 (4).

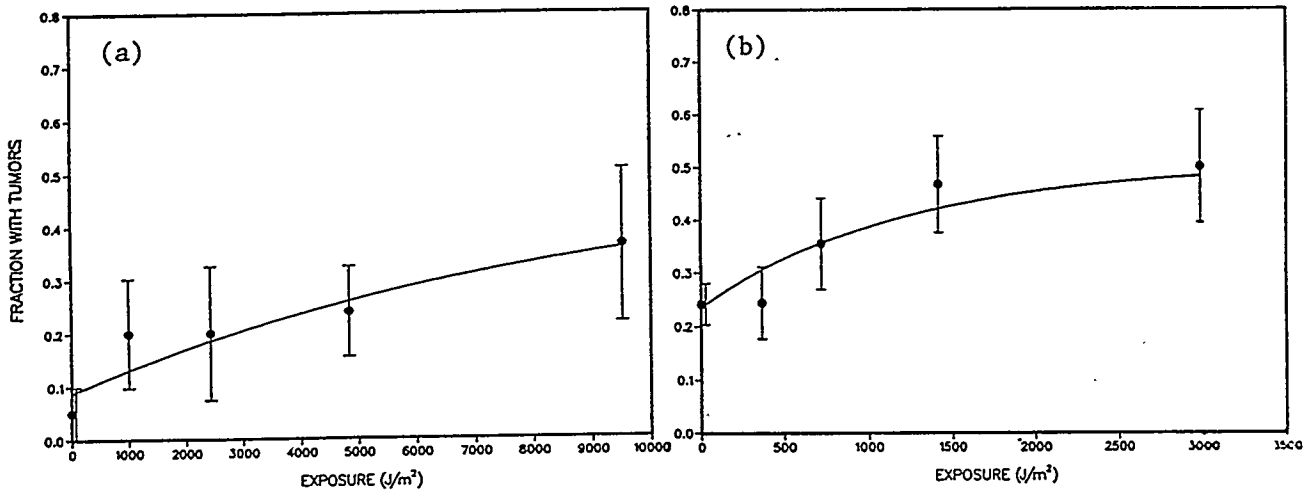

Figure 1: Fluence response curves for melanoma induction in hybrid fish by a) 405 nm, and b) 313 nm. The errors are standard deviations. The background level at 405 nm is less than at 313 nm. The latter experiment used fish maintained in the ambient light of a shaded greenhouse. The former used in tanks screened, for two months, by yellow plastic. We interpret the difference as indicating that visible light is effective in melanoma induction.

The sensitivities at the other wavelengths tested, relative to the value of 1.00 at 302 nm, are given in Fig. 2a, along with the action spectrum for human erythema and the mid-summer sun's spectrum at 41°N latitude. The melanoma sensitivity in the UVA region is orders of magnitude greater than for erythema, and sunlight contains much more UVA than UVB. The product of the sun's spectrum multiplied by the action spectrum is the relative sunlight dose as a function of wavelength (Fig. 2b). If the human action spectrum were similar to the fish spectrum, UVB would contribute only 5 to 10% of the melanoma inducing effect and 90 to 95% could be ascribed to UVA and visible. Hence, O_3 depletion would have a negligible effect on melanoma incidence. The high sensitivity to UVA may be explained by free radicals or other activated products formed in melanin which then may affect cellular DNA. Since most sunscreens absorb much more UVB than UVA (5). Individuals who use UVB sunscreens and increase their exposure time to the sun, would increase their UVA carcinogenesis dose. An 8-fold increase in exposure time by an individual using an SPF 8 UVB sunscreen would result in a 5 to 6-fold increase in melanoma inducing dose. Hence, the habits of sun exposure, especially the use of sunscreens, would greatly increase the melanoma inducing dose and could be responsible for the melanoma epidemic and exponential increase---~ 5% a year for 40 or more years.

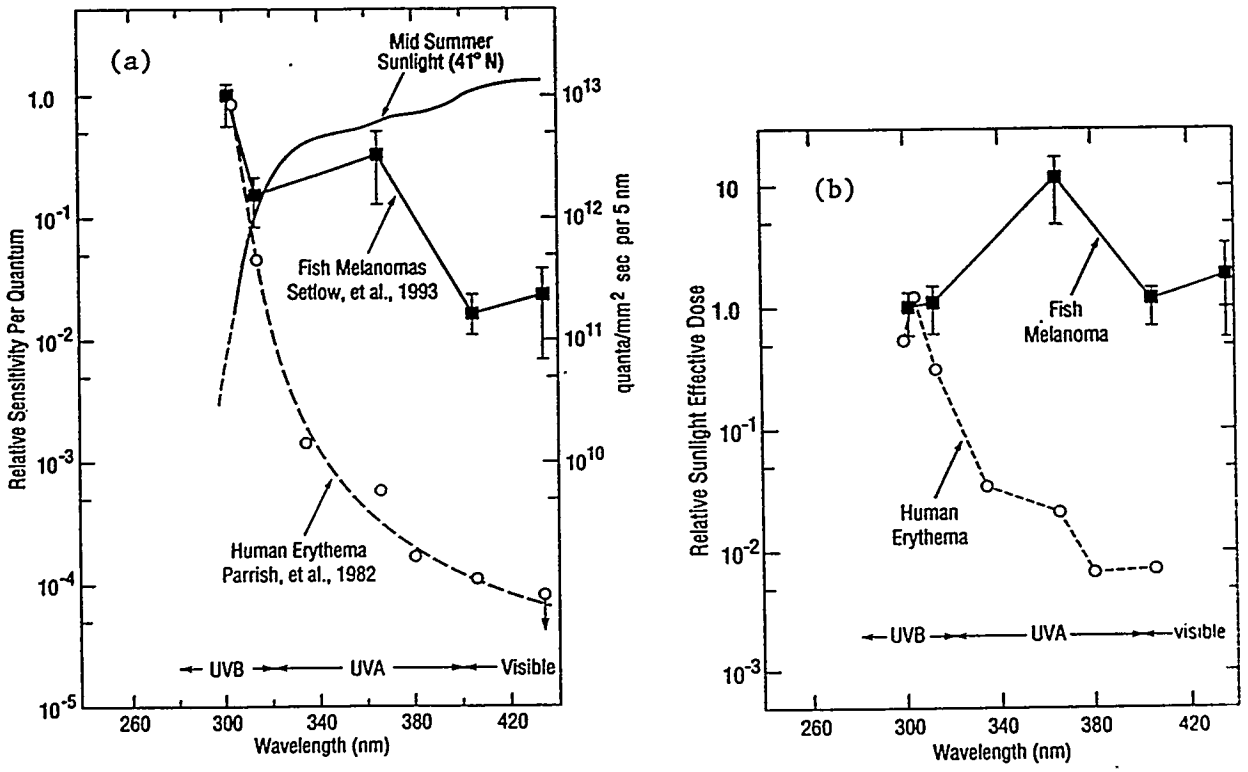

Figure 2: a) Action spectra for melanoma induction and human erythema normalized to 1.00 at 302 nm. Note the exponential sensitivity scale. b) The relative sunlight effective dose versus wavelength.

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References

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2. Setlow, R. B., Woodhead, A. D., and Grist, E. (1989) Animal model for ultraviolet radiation-induced melanoma: Platyfish-swordtail model. Proc. Natl. Acad. Sci. USA 86, 8922-8926. A description of useful animal models--Xiphophorus maculatus x Xiphophorus helleri backcross hybrids that develop malignant melanomas within 4 months of exposure to sunlamp radiation > 290 nm or > 304 nm delivered as one or 20 treatments. Exposure of the fish to visible fluorescent light after UV reduces the tumor prevalence to background levels.
3. Setlow, R. B., Grist, E., Thompson, K., and Woodhead, A. D. (1993) Wavelengths effective in induction of malignant melanoma. Proc. Natl. Acad. Sci. USA 90, 6666-6670. The fish model, described in ref. 2, was used to determine the melanoma susceptibility to single exposures to 302, 313, 365, 405, and 436 nm (see Fig. 2a).
4. Parrish, J. A., Jaenicke, K. F., and Anderson, R. R. (1982) Erythema and melanogenesis action spectra of normal human skin. Photochem. Photobiol. 36, 187-191. Data from 250 nm to 405 nm (see Fig. 2a). Note that the values of the ordinate in Fig. 1a of this reference are too large by a factor of 10.
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